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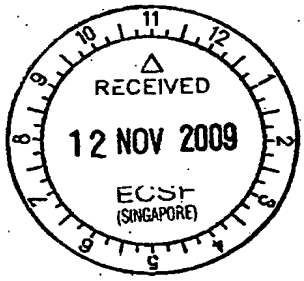

Your Ref : 20722SG37/KJR/EVA/PAC
Our Ref 2007048978/091109/TMMHO/7332
Date : 09/11/2009
Writer's Direct Line : 63302748

ELLA CHEONG SPRUSON & FERGUSON (SINGAPORE) PTE LTD
P.O. BOX 1531
ROBINSON ROAD POST OFFICE
SINGAPORE 903031

Dear Sir,

Singapore Patent Application No.: 200704897-8
Title of invention: METHODS OF GENERATING AND SCREENING FOR PROTEASES WITH ALTERED SPECIFICITY
Applicant(s): CATALYST BIOSCIENCES, INC. (US)
REGENTS OF THE UNIVERSITY OF CALIFORNIA (US)

INVITATION TO RESPOND TO WRITTEN OPINION

We forward with this letter a copy of the Written Opinion drawn up by the Examiner in connection with your request for an Examination Report.

You are invited to respond to the opinion by submitting:

(a) Written submissions or arguments disagreeing with the Examiner's opinion and/or
(b) An amendment of the specification of the application.

If you intend to respond, the response must be filed within 5 months from the date of this letter. You are also advised to inform us early if you do not intend to respond.

The Examiner will proceed to establish the Examination Report if no response is received by the end of the prescribed period.

If you have any further queries, please do not hesitate to contact the undersigned.

Thank you.

Yours faithfully,

Muhammad Haramain Osman
for REGISTRAR OF PATENTS
SINGAPORE

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Intellectual Property Office of Singapore
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SINGAPORE 189554

16 OCT 2009

Attention: Registrar

RE: Singapore Application/Patent No. **0704897-8**

In the Name of: **Catalyst Biosciences, Inc. (US)**
Regents of The University of California

Please find attached the relevant completed:

- [ ] Search Report
- [ ] Examination Report
- [x] Written Opinion 2nd
- [ ] Revocation/Re-examination Advisory Report
- [ ] Allowability of Opposed Amendments Advisory Report
- [ ] Infringements Advisory Report

and

- [ ] Citation/Annexes
- [ ] Priority Document and Citations (Singapore Office Copy)
- [ ] Invoice

Mathew FISHER
PCT Unit

Facsimile: 61 2 6283 7999
E-mail: pct@ipaustralia.gov.au

06/10/09

AUSTRALIAN PATENT OFFICE

WRITTEN OPINION

175175

	Date of mailing *day/month/year* 6 OCT 2009
Applicant's or agent's file reference 20722SG37/KJR/EVA/pac	**REPLY DUE** within FIVE MONTHS of the date of the Registrar's letter enclosing the written opinion

Application No.	Parent Filing Date *(day/month/year)*	Priority Date *(day/month/year)*
SG 200704897-8	2 October 2003	2 October 2002

International Patent Classification (IPC)

Int. Cl.

G01N 33/573 (2006.01)

Action Date: 30 September 2009

Applicant

CATALYST BIOSCIENCES, INC. et al

1. This second written opinion consists of a total of 6 sheets.

2. This opinion contains indications relating to the following items:.

G00001

I	[X]	Basis of the opinion
II	[ ]	Priority
III	[ ]	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	[ ]	Lack of unity of invention
V	[X]	Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	[ ]	Certain documents cited
VII	[ ]	Certain defects in the application
VIII	[X]	Certain observations on the application

ACTION

3. The search report used was issued by the **Australian Patent Office**, and the date of completion is: **23 February 2009**

4. If no reply is filed, the examination report will be established on the basis of this opinion.

5. The date by which the examination report will be established is: **29 September 2011**

Name and mailing address	Authorized Officer
AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile no. 61 2 62853929	**Sonita Singh**

Form APO/SG/408 (Cover Sheet)(Dec 2006)

AUSTRALIAN PATENT OFFICE

WRITTEN OPINION

Application No.
SG 200704897-8

I. Basis of the opinion

1. This opinion has been drawn on the basis of:

☐ the application as originally filed.

☒ the description, pages **1-54** , as originally filed,
pages , as amended under Art. 34 of the PCT
pages , filed with the request,
pages , received on with the letter of

☒ the claims, pages , as originally filed,
pages , as amended under Art. 19 of the PCT
pages , as amended under Art. 34 of the PCT
pages , filed with the request,
pages **55, 55a, 56, 56a, 57, 57a, 58, 58a, 58b, 58c and 59** , received on **28 August 2009**
with the letter of **28 August 2009**

☒ the drawings, sheets/fig. **1/7-4/7 and 6/7-7/7** , as originally filed,
sheets/fig. , as amended under Art. 34 of the PCT
sheets/fig. , filed with the request,
sheets/fig. **5/7** , received on **25 July 2007** with the letter of **25 July 2007**

☐ the sequence listing part of the description:

pages , as originally filed
pages , as amended under Art. 34 of the PCT
pages , filed with the demand
pages , received on with the letter of

2. The amendments have resulted in the cancellation of: pages:
sheets of drawings/figures No :

3 ☐ This opinion has not been established in relation to,

description pages
claim nos
drawings sheets/figs

since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box

4. Additional observations, if necessary:

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WRITTEN OPINION

Application No.
SG 200704897-8

V. Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims **1-30**	YES
	Claims **None**	NO
Inventive step (IS)	Claims **None**	YES
	Claims **1-30**	NO
Industrial applicability (IA)	Claims **1-30**	YES
	Claims **None**	NO

2. Citations and explanations

The following documents identified in the Search Report have been considered for the purposes of this report:

D1: HARRIS, J. L. et al, The Journal of Biological Chemistry, 1998, Vol. 273, No. 42, pages 27364-27373
D2: BORNSCHEUER, U. T. et al, Current Opinion in Chemical Biology, 2001, Vol. 5, No. 2 pages 137-143.
D3: OLSEN, M. et al, Current Opinion in Biotechnology, 2000, Vol. 11, No. 4 pages 331-337.
D4: GUPTA, R. et al, Applied Microbiology and Biotechnology, 2002, Vol. 59, No. 1, pages 15-32.
D5: BIANCHI, E. et al, Biopolymers (Peptide Science), 2002, Vol. 66, pages 101-114.
D6: US 5766842 A 16 June 1998
D7: CASCIOLA-ROSEN, L. et al, J. Exp. Med, September 1999, Vol. 190, No. 6, pages 815-825

The following new citation has also been identified:

D8: LIEN, S. et al, "Combinatorial Strategies for the Discovery of Novel Protease Specificities", Combinatorial Chemistry & High Throughput Screening, 1999, Vol. 2, pages 73-90

The current application is directed towards a method of identifying a modified protease which involves production of a library of mutant proteases and selection of proteases from that library that cleave and deactivate a target protein with increased activity or specificity wherein the target protein is involved with a pathology or disease.

NOVELTY (N)

None of the prior art documents D1-D8 explicitly discloses the method defined by the current claims. Therefore the subject matter of claims 1-30 is new and meets the requirements of Section 14 of the Singapore Act with regard to novelty.

D1 is directed toward the identification of Granzyme B substrates during cell apoptosis. The preferred substrate sequence is found to match the activation site of caspase 3 and caspace 7. One of the methods disclosed involves production of two mutated variants of Granzyme B protease and testing of their activity and specificity by screening them against substrate peptides (see page 27365 column 2, Figure 2, Table III and Table V). The two variants could be considered a library of proteases according to the current claims and the preferred substrate sequence matches the activation site of caspase 3 and caspace 7 which are considered to be the target proteins. However the mutants are not found to have increased activity or specificity toward the target protein and the proteases do not inactivate the target substrate protein. Therefore the method is not within the method defined by the current claims.

[Continued in Supplemental Box A]

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VIII. Certain observations on the application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

[X] The claimed invention is patentable according to Section 13(2); or

[ ] The claimed invention is unpatentable according to Section 13(2) because:

[X] This application is a Divisional application filed under Section 26(6) of the Patents Act and discloses no additional matter extending beyond that disclosed in the Parent application.

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WRITTEN OPINION

Application No.
SG 200704897-8

Supplemental Box A
(To be used when the space in any of Boxes I to VIII is not sufficient)

Continuation of Box [No.]: V

D2-D4 each disclose methods for directed evolution of proteins by selection from libraries of mutated proteins based on their activity. However, all examples presented relate to industrial proteases and biocatalysts. None of the examples relate to proteases which target proteins associated with disease.

D5 discloses methods for selecting viral protease inhibitors from a library of peptides. However the inhibitor peptides are not themselves proteases.

D6 discloses selection of HIV-1 protease mutants from a library based on their activity, to model natural protein mutation which could lead to drug resistance. The method of the current claims is different to this method because the protease activity and/or specificity is measured quantitatively to identify those with increased activity and/or specificity whereas in the prior art mutants are identified only as being active or not active. The activity is not measured quantitatively.

D7 is a study of Granzyme B protease cleavage. The protease is not modified.

D8 describes methods for generating novel cleavage specificities in serine proteases using combinatorial mutagenesis (see Abstract). The methods are taught to be useful in medical applications and therapy, however, no specific methods for producing a protease that will inactivate a protein involved in a disease or pathology are explicitly disclosed.

INVENTIVE STEP (IS)

The subject matter of claims 1-30, which relate to broad and general methods for identifying a modified protease that cleaves a substrate in a target protein, does not involve an inventive step in view of any one of D2-D4 and D8.

D2 teaches the basic methodology for directed evolution of a protein which includes producing a library of mutated forms of the protein followed by analysis to identify the improved variants (see Introduction, 3rd aragraph and Figure 1). Also disclosed is the phage display technique and digital screening of fluorescent products (see page 139).

D3 is directed towards high-throughput screening methods for directed evolution of enzymes for industry and medicine. The basic process of directed evolution is outlined to involve creating a population of mutant enzymes and applying selective pressure such that those mutants that express a particular function are selected (see Introduction). It is taught that the process is typically applied in an iterative fashion until the desired result is achieved. The screening methodologies described include phage display (see pages 333-334) and detection of fluorescent products (see page 335 and Figure 3).

D4 is directed to approaches to improving bacterial alkaline proteases for industrial use including directed evolution (see Abstract and pages 22-23) It teaches that directed evolution is a key technology to generate enzymes with new and improved properties. While medical applications are not mentioned, a person skilled in the art would realise that the same techniques apply to any protease regardless of the purpose.

D8 describes methods for generating novel cleavage specificities in serine proteases using combinatorial mutagenesis with applications in academia, industry and medicine (see Introduction). Phage display techniques are disclosed (see page 80-81 and 85-87) as well as cleavage measurement based on fluorescence (see page 84).

The only difference between the methods of the prior art documents D2-D4 and D8 and the current claims is that the current claims specify that the protease should inactivate a target protein involved in a disease or pathology. The claims are therefore defined by a desired result rather than by any technical features of the method. This desired result of producing a protease which targets a protein that causes disease is considered obvious since many known proteins are associated with disease. It would be obvious to a person skilled in the art to employ the known methods described in the prior art in order to produce such a protease.

[Continued in Supplemental Box B]

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WRITTEN OPINION

Application No.
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Supplemental Box B
(To be used when the space in any of Boxes I to VIII is not sufficient)

Continuation of Box [No.]: V

The claims do not define any specific technical features but only general methods and possible target proteins known to be associated with diseases. The description reveals no specific advantages or surprising results which apply to the full scope of the method defined in the current claims. Neither does the description reveal any technical difficulties overcome in arriving at this method. Therefore the subject matter of claims 1-30 is obvious in and does not meet the requirements of Section 15 of the Singapore Act with regard to inventive step.

INDUSTRIAL APPLICABILITY (IA)

The invention defined in claims 1-23 is considered to meet the requirements of Industrial Applicability under Section 16 of the Singapore Act because it can be made by, or used in, industry.